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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 340624/18032	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR00/00430	International filing date (*day/month/year*) 21 February 2000 (21.02.00)	Priority date (*day/month/year*) 22 February 1999 (22.02.99)
International Patent Classification (IPC) or national classification and IPC C12N 7/02, B01D 15/08, B01J 8/18		
Applicant TRANSGENE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 September 2000 (11.09.00)	22 May 2001 (22.05.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR00/00430

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-30, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 1-11, filed with the letter of 07 July 2000 (07.07.2000)

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR 00/00430

I. Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

The amendments submitted with the letter of 7 July 2000 do not appear to extend beyond the invention in the application as filed (PCT Article 34(2)(b)).
The new set of Claims 1-11 is considered acceptable and will be used for the rest of the examination.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-11	NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following documents:

D1: WO-A-96/27677 (CANJI INC) 12 September 1996 (1996-09-12)

D2: WO-A-97/08298 (GENZYME CORP; RIORDAN CATHERINE E O (US); ERICKSON AMY E (US); SMI) 6 March 1997 (1997-03-06)

D3: WO-A-97/06243 (PASTEUR MERIUX SERUMS VACC; FANGET BERNARD (FR); FRANCON ALAIN (F)) 20 February 1997 (1997-02-20)

D4: US-A-5 522 993 (GUSTAFSSON JAN-GUNNAR ET AL) 4 June 1996 (1996-06-04) cited in the application

D5: HARUNA I ET AL: 'SEPARATION OF ADENOVIRUS BY CHROMATOGRAPHY ON DEAE-CELLULOSE' VIROLOGY, Vol. 13, 1 January 1961 (1961-01-01), pages 264-267, XP000601693 ISSN: 0042-6822.

Document cited by the examiner (a copy is attached):

D6: Hjorth R.: 'Expanded-bed adsorption in industrial bioprocessing: recent developments' Trends Biotechnol. 1997, June 15(6): 230-5.

2. Novelty (PCT Article 33(2))

The purification process involving an adsorption step in a fluidized bed (also known as "Expanded-Bed Adsorption" or "EBA") is known in the field of protein or oligonucleotide purification. However, none of the prior art documents cited in the search report mentions the use of this particular technique for purifying a viral preparation. Claims 1-11 are considered novel within the meaning of PCT Article 33(2).

3. Inventive step (PCT Article 33(3))

Document D2 describes adenovirus or AAV purification (for use in genetic therapy) using conventional chromatography methods (using suitable conventional resins in a "batch" or "flow-through" process, with the aim of preventing damage to the viral particle, see D2, pages 4-6).
The difference between the present application and D2 is the use of a novel chromatography step, namely a method using an "expanded-bed" adsorption step.
The technical problem is that of finding an alternative method for purifying a viral preparation, which method can be used in the field of genetic therapy.

The particular expanded-bed adsorption chromatography technique is known (cf. D4) and is used in the field of protein purification, as disclosed in document D6 as well.
The viral preparations are generally purified using "conventional" chromatography steps (cf. the examples in documents D1-D3 and D5).

However, it is known in the art that purification of biological material must be carried out as quickly as possible to prevent any degradation and thus optimize the possibility of maintaining the integrity of the biological material to be separated. Similarly, the cellular debris generated by lysis of the cell lines producing viral particles is also known for its tendency to clog the conventional chromatography columns. The use of "expanded-bed" adsorption for purifying viral vectors is mentioned in D1. Moreover, D6 clearly mentions the advantages of said expanded-bed adsorption chromatography technique for the clarification of cellular homogenates, the high speed of substance purification as well as the use of similar equipment to that used in conventional chromatography. For example, the known groupings used in ion exchange techniques in conventional chromatography are used for expanded-bed adsorption chromatography. Similarly, affinity chromatography, which is known to be effective for purifying viral particles in conventional chromatography (cited in D2, page 6), also uses expanded-bed techniques (antibody purification mentioned in D6).

Apart from having a larger size on the atomic scale, these viral particles consist of a complex assembly of viral proteins protecting the genetic material of the virus and are regulated by the same physical-chemical rules as more simple molecules (such as recombinant proteins or oligonucleotides purified using "EBA", as in the prior art).

A person skilled in the art would therefore be led to use this information in order to combine the advantages of the two techniques and thus arrive at an "affinity" or "conventional" expanded-bed

adsorption chromatography step for purifying a viral preparation. In the absence of any unexpected effect, the separation conditions and parameters used are known to a person skilled in the art and do not appear to involve an inventive step.

Therefore, a person skilled in the art seeking to solve the technical problem would be led to combine the conventional chromatography separation techniques known in the field of purifying viral particles with the techniques involving an "expanded-bed" adsorption step (the advantages of which are known in the field of macromolecule purification) in order to develop an alternative method for purifying a viral preparation. Therefore, the subject matter of Claims 1-11 does not appear to involve an inventive step (PCT Article 33(3)).